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Citation

Mitra, Devarati, Paul J. Catalano, Nicole Cimbak, Antonio L. Damato, Michael G. Muto, and Akila N. Viswanathan. 2016. "The risk of lymphedema after postoperative radiation therapy in endometrial cancer." *Journal of Gynecologic Oncology* 27 (1): e4. doi:10.3802/jgo.2016.27.e4. <http://dx.doi.org/10.3802/jgo.2016.27.e4>.

Published Version

doi:10.3802/jgo.2016.27.e4

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Original Article



The risk of lymphedema after postoperative radiation therapy in endometrial cancer

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Received: Apr 17, 2015

Revised: Aug 16, 2015

Accepted: Sep 13, 2015

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ABSTRACT

Objective: Lower extremity lymphedema adversely affects quality of life by causing discomfort, impaired mobility and increased risk of infection. The goal of this study is to investigate factors that influence the likelihood of lymphedema in patients with endometrial cancer who undergo adjuvant radiation with or without chemotherapy.

Methods: A retrospective chart review identified all stage I–III endometrial cancer patients who had a hysterectomy with or without complete staging lymphadenectomy and adjuvant radiation therapy between January 2006 and February 2013. Patients with new-onset lymphedema after treatment were identified. Logistic regression was used to find factors that influenced lymphedema risk.

Results: Of 212 patients who met inclusion criteria, 15 patients (7.1%) developed new-onset lymphedema. Lymphedema was associated with lymph-node dissection (odds ratio [OR], 5.6; 95% CI, 1.01 to 105.5; $p=0.048$) and with the presence of pathologically positive lymph nodes (OR, 4.1; 95% CI, 1.4 to 12.3; $p=0.01$). Multivariate logistic regression confirmed the association with lymph-node positivity (OR, 3.2; 95% CI, 1.0007 to 10.7; $p=0.0499$) when controlled for lymph-node dissection. Median time to lymphedema onset was 8 months (range, 1 to 58 months) with resolution or improvement in eight patients (53.3%) after a median of 10 months.

Conclusion: Lymph-node positivity was associated with an increased risk of lymphedema in endometrial cancer patients who received adjuvant radiation. Future studies are needed to explore whether node-positive patients may benefit from early lymphedema-controlling interventions.

Keywords: Endometrial Neoplasms; Lymphedema; Positive Lymph Nodes

Funding

Dr. Viswanathan receives funding from National Institutes of Health R21 167800.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

This study was presented in part at the American Society for Therapeutic Radiation Oncology Annual Meeting in San Francisco on September 15, 2014.

INTRODUCTION

Lower-extremity lymphedema is a known possible complication of endometrial cancer treatment that adversely affects quality of life [1,2]. Prior single-institution retrospective studies have reported lymphedema rates that vary greatly from 2% to 47% [1-8]. Notably, the number of lymph nodes removed varied greatly among these studies, with the lowest rates of lymphedema (2.4% to 11.4%) reported in studies where most patients had fewer than 10 lymph nodes removed, and the highest rates (27.2% to 47%) reported in studies where most patients had more than 20 lymph nodes removed [3-6,8,9]. A recent survey of the Australian National Endometrial Cancer Study Group found that 13% of 1,243 patients treated for endometrial cancer developed self-reported or physician-reported lymphedema. In that study, the absolute risk of lymphedema in patients with no lymph nodes removed was 8% or less whereas the risk in patients with more than 15 lymph nodes removed was over 30% [10]. In this study and in others, a variety of other risk factors for lymphedema after endometrial cancer treatment have also been suggested, including radiation, chemotherapy, and nonsteroidal anti-inflammatory drug use; however, the strength of correlation and magnitude of these effects are typically less pronounced than the effect of lymph node dissection [6,8,10].

Whether factors other than lymphadenectomy may increase the risk of lymphedema has not been well established. In addition, once lymphedema develops, the expected clinical course is not well understood. The goal of the current study is to investigate patient, disease, and treatment factors that may be associated with lymphedema development in endometrial cancer patients who received adjuvant external beam radiotherapy and vaginal brachytherapy after hysterectomy, and to characterize the clinical course of this complication.

MATERIALS AND METHODS

Retrospective chart review identified 222 patients with stage I–III endometrial cancer who received adjuvant radiation after hysterectomy between January 2006 and February 2013, were not on a trial of bevacizumab, and had more than 1 year of follow-up data available. Of these, 10 patients had disease recurrence less than 3 months after radiation therapy and were therefore excluded, resulting in the data from 212 patients being used for analysis.

The medical record of each patient was examined to collect patient characteristics (including age, body mass index [BMI] and Charlson comorbidity index), disease characteristics (including stage, grade, myometrial invasion, lymphovascular invasion, pelvic washings, and positive lymph nodes found upon surgery), detailed treatment parameters (including number of lymph nodes removed, total external beam radiation dose including a boost if present, vaginal brachytherapy dose, length of radiation treatment, and type of chemotherapy regimen), and disease outcomes (including disease recurrence and mortality).

All patients underwent computed tomography-based planning with custom immobilization. External beam radiation was administered in daily treatments 5 days per week in 1.8 Gy daily fractions to the pelvis with 15 MV photons; some patients also received concurrent 1.2 to 1.5 Gy to the whole abdomen (anterior-posterior/posterior-anterior technique or intensity modulated radiation therapy [IMRT]) for 20 to 25 fractions with 6 MV. Patients with para-

aortic nodal disease received IMRT consisting of 7 to 9 fields, using 6 MV photons with dose limits as previously described [11].

The medical record was also used to identify patients with new-onset lower extremity lymphedema, as described by the physician or reported by the patient. The medical records of each patient with lymphedema were carefully examined to confirm that the onset of this symptom was subsequent to cancer treatment and not attributable to an independent pre-existing etiology, such as heart failure. Due to the retrospective nature of this study, precise measurements of lymphedema were not available. However, it is standard practice in our clinic to ask all patients who have had endometrial-cancer treatment whether they have noted new lower-extremity swelling as well as to formally evaluate this by both visual inspection and palpation.

For patients who developed new-onset lymphedema, the medical record was used to track the clinical course of this complication. Specifically recorded were: time from treatment completion to onset; subsequent progression, improvement or resolution (as documented by a physician at follow-up visits); time to resolution (if present); and the documented interventions used to treat lymphedema.

Statistical analyses were performed using JMP (SAS Institute, Cary, NC, USA). For each demographic, disease and treatment parameter, univariate logistic regression was used to estimate the odds ratio (OR) of association with lymphedema. For parameters that had a statistically significant ($p < 0.05$) association with lymphedema, a multivariate logistic model was created using stepwise selection. In the final analysis, parameters were considered significant with a two-sided $p < 0.05$. This study was approved by the Institutional Review Board of the Dana Farber/Brigham & Women's Cancer Center.

RESULTS

1. Patient, disease, and treatment characteristics

The records of the 212 endometrial cancer patients who received adjuvant radiotherapy after hysterectomy and met the inclusion criteria were reviewed. Patient, disease, and treatment characteristics as well as disease outcomes are described in **Table 1**. The population represented a wide spectrum of intermediate- to high-risk disease. Most patients had either endometrioid or papillary serous histology (81.6%), which manifested as mostly grade 2–3 disease (76.9%). Approximately half of patients had lymphovascular invasion and half had deep (more than 50%) myometrial invasion. Pelvic lymph-node dissection was performed in 75% ($n=159$) with a median of 6.5 (range, 0 to 58) pelvic lymph nodes removed. Notably, only 11.3% ($n=24$) had more than 20 lymph nodes removed. All patients received adjuvant radiation, consisting most commonly of 45 Gy external beam radiotherapy (80.7%) followed by 16 Gy (4 fractions of 4 Gy) vaginal brachytherapy (94.8%). Adjuvant chemotherapy was received by slightly more than half of patients, with carboplatin and taxol being used most commonly. Disease recurred in 23.6% of patients, with many having simultaneously detected recurrence at multiple sites. Overall, no patients had an isolated vaginal recurrence, 4.7% had recurrence in a pelvic lymph node, 9.0% had regional recurrence (para-aortic or pelvic side-wall), and 17.0% had recurrence at a distant site.

Table 1. Study population demographic, disease, treatment, and outcome characteristics

Characteristic	Value
Study population	
Enrollment period	2006–2013
Total patients receiving treatment	264
Patients excluded from analysis	52
<1 yr follow-up from diagnosis	24
Stage IV disease on presentation	14
Recurrence <3 mo after treatment	10
Patients enrolled in bevacizumab trial	4
Total patients eligible for analysis	212
Patient characteristic	
Age (yr)	64 (34–91)
Body mass index (kg/m ²)	29.8 (17–63)
Charlson comorbidity index	0 (0–4)
Follow-up from diagnosis (mo)	35 (12–84)
Treatment characteristic	
Lymph node dissection	159 (75.0)
0	53 (25.0)
1–9	67 (31.6)
≥10	92 (43.4)
Adjuvant chemotherapy	120 (56.6)
Carboplatin/paclitaxel	98 (46.2)
Oxaliplatin/gemcitabine	10 (4.7)
Concurrent cisplatin/radiation	12 (5.7)
External beam radiation dose (Gy)	212 (100)
41.4	1 (0.5)
45	171 (80.7)
50–50.4	21 (9.9)
54–64.8	19 (9.0)
Vaginal brachytherapy (Gy)	212 (100)
12–15	10 (4.7)
16	201 (94.8)
18	1 (0.5)
Time elapsed during radiation (day)	56 (38–103)
Disease characteristic	
Initial FIGO stage	
I	72 (34.0)
II	48 (22.6)
IIIA/B	37 (17.5)
IIIC	55 (25.9)
Initial histology	
Endometrioid	127 (59.9)
Uterine papillary serous	46 (21.7)
Uterine clear cell	7 (3.3)
Uterine carcinosarcoma	26 (12.3)
Uterine squamous	6 (2.8)
Initial grade	
1	49 (23.1)
2	57 (26.9)
3	106 (50.0)
Myometrial invasion (%)	
0–25	70 (33.0)
26–50	42 (19.8)
51–75	53 (25.0)
>75	47 (22.2)
Lymphovascular invasion	16 (54.7)
Positive pelvic washings	35 (16.5)
Positive pelvic lymph nodes	52 (24.5)
Positive para-aortic lymph nodes	12 (5.7)
Disease outcome	
Disease recurrence at any site	50 (23.6)
Pelvic node recurrence	10 (4.7)
Mortality	26 (12.3)
Cancer related mortality	20 (9.4)

Values are presented as number, median (range), or number (%).
 FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Detailed characteristics of patients with new-onset lymphedema

Patient			Disease characteristic						Treatment characteristic				Lymphedema course			
ID	Age (yr)	Follow-up (mo)	Histology	Grade	Stage	MI (%)	LVI	Recurrence site (mo)	No. of pelvic LN dissected	(+) Pelvic LN	EB dose (Gy)	Chemotherapy	Time to onset (mo)	Change in LE	Tx	Duration (mo)
1	68	79	PS	3	IA	25	N	Lung (49)	6	0	45*	N	1	Resolve	Y	11
2	77	30	CS	3	IA	30	Y	N	11	0	45*	carb/tx	7	Resolve	N	15
3	77	74	CS	3	IA	33	N	N	24	0	45*	oxalip/gem	26	Worsen	Y	>38
4	66	26	Endo	1	IB	90	Y	N	0	0	45*	N	15	Improve	N	>7
5	86	41	CS	3	IB	60	N	N	1	0	45*	N	6	Resolve	Y	9
6	76	59	CC+Endo	3	IB	90	Y	N	16	0	45*	N	15	Resolve	N	4
7	53	48	Endo	3	IIIA	5	N	N	7	0	45*	carb/tx	13	Stable	Y	>34
8	61	64	Endo	1	IIIC1	40	Y	N	5	1	45 [†]	carb/tx	48	Improve	N	>3
9	58	70	Endo	2	IIIC1	40	N	N	18	1	45*	carb/tx	4	Resolve	Y	6
10	59	69	Endo	1	IIIC1	55	Y	N	19	1	45 [†]	N	58	Stable	Y	>11
11	63	33	Endo	1	IIIC1	50	Y	N	11	1	45*	carb/tx	1	Resolve	Y	13
12	72	24	PS+CC	3	IIIC1	65	Y	Pelvic LN (16)	15	2	61.2 [‡]	carb/tx	8	Stable	Y	>7
13	56	29	Endo	2	IIIC1	0	N	N	29	2	45*	carb/tx	1	Stable	Y	>19
14	78	24	CS	3	IIIC1	95	N	Lung (16)	22	3	50.4*	carb/tx	3	Stable	Y	>9
15	61	43	Squamous	3	IIIC2	100	Y	N	3	3	55.8 [‡]	carb/tx	15	Stable	N	>17

carb/tx, carboplatin/paclitaxel; CC, clear cell; CS, carcinosarcoma; EB, external beam radiotherapy; Endo, endometrioid; LE, lymphedema; LN, lymph nodes; LVI, lymphovascular invasion; MI, myometrial invasion; N, no or absent; oxalip/gem, oxaliplatin/gemcitabine; PS, papillary serous; Tx, lymphedema treatment; Y, yes or present; (+), tumor positive.

*4-field pelvis. [†]Whole abdomen anterior-posterior/posterior-anterior. [‡]Intensity modulated radiation therapy to pelvis and para-aortic nodes.

2. Onset and management of lymphedema

With a median follow-up time of 35 months (range, 12 to 84 months), 7.1% of patients (n=15) developed new-onset lower-extremity lymphedema. **Table 2** describes the detailed demographic, disease, and treatment characteristics of each patient who developed lymphedema as well as the clinical course of this symptom. The median time to onset of documented lymphedema, measured from the last day of radiation therapy, was 8 months (range, 1 to 58 months) with six patients (40.0%) having complete resolution of their lymphedema a median of 10 months (range, 4 to 15 months) later, two patients (13.3%) having some improvement, six patients (40.0%) having stable symptoms, and one patient (6.7%) experiencing worsening lymphedema over time. Two-thirds (n=10) of the patients with lymphedema were documented to have received compression stockings and 3 were also documented to have received therapeutic lower-extremity massage. Information regarding the details of the massage technique were not available. However, no correlation was found between documented intervention and improvement or resolution of symptoms. There was no difference in the characteristics of patients who had resolution of symptoms and those who did not; characteristics examined included BMI, age, Charlson comorbidity index and time interval from treatment completion to lymphedema onset.

3. Incidence and prevalence of lymphedema

The incidence and prevalence of lymphedema over time is illustrated in **Fig. 1**. Of the 15 patients who developed lymphedema after treatment, 80.0% (n=12) developed the symptom within 18 months of completing therapy. Three additional patients developed new lymphedema later (26, 48, and 58 months after treatment completion). An early peak prevalence of lymphedema occurred by 15 months after treatment followed by a decline that plateaued at 25 months and subsequently slowly rose at much later time points to a final peak prevalence of 4.3% at 5 years after treatment.

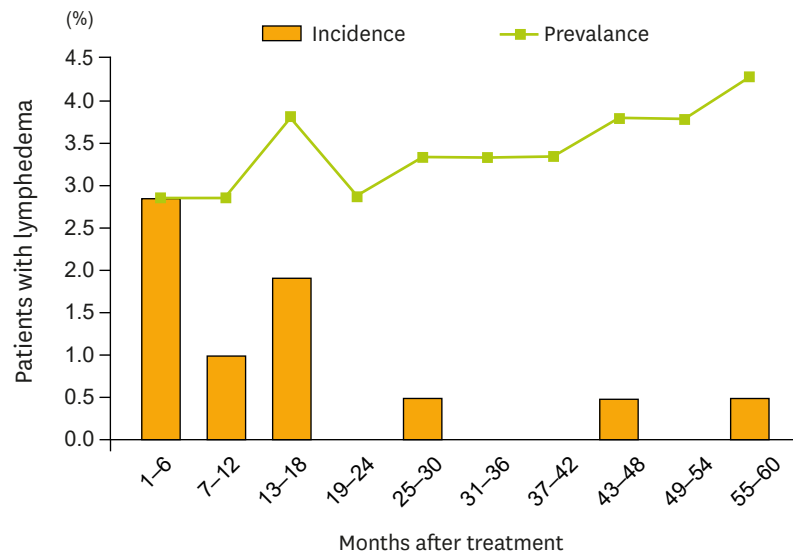


Fig. 1. Incidence and prevalence of lymphedema. Bar graph shows the percent of patients with new onset lymphedema during each 6-month interval after adjuvant therapy completion. Line graph shows the prevalence of lymphedema during the same time period.

4. Risk factors for lymphedema

Univariate logistic regression was performed to investigate possible factors that influence the risk of lymphedema after endometrial-cancer treatment. **Table 3** illustrates the ORs of lymphedema by disease and treatment characteristic tested. Having a more complete pelvic lymph node dissection (defined as 10 or more lymph nodes removed) was associated with an increased risk of lymphedema when compared to no dissection (OR, 5.6; 95% CI, 1.01 to 105.5; $p=0.048$). However, a less complete lymph-node dissection (defined as 1 to 9 lymph nodes removed) was not associated with increased risk ($p=0.14$). The cut-off of 10 lymph nodes as the break-point for analysis was chosen because the mean number of lymph nodes removed in our study was 9.7; 56.6% of patients who had any nodes dissected had 1 to 9 lymph nodes removed and 43.4% had 10 or more removed (**Table 1**). Of the 15 patients who developed lymphedema, 1 (6.7%) had no lymph nodes removed, 5 (33.3%) had fewer than 10 lymph nodes removed, and 9 (60.0%) had 10 or more lymph nodes removed.

Table 3. Predictors of lymphedema by univariate and multivariate models

Characteristic	Odds ratio	
	Univariate model	Multivariate model
Patient characteristic		
Age (yr), >70 vs. ≤70	0.8 (0.2–2.6)	
Body mass index (kg/m ²), >25 vs. ≤25	1.0 (0.2–3.8)	
Charlson comorbidity index, >2 vs. 0–2	1.7 (0.2–14.5)	
Disease characteristic		
Lymphovascular invasion, yes vs. no	0.9 (0.3–2.7)	
Disease recurrence, yes vs. no	0.80 (0.2–2.9)	
Pelvic lymph nodes, with disease vs. no disease	4.1 (1.4–12.3)*	3.2 (1.0007–10.7)*
Treatment characteristic		
LND, ≥10 LN removed vs. no LN removed	5.6 (1.01–105.5)*	3.1 (0.4–26.8)
External beam radiation (Gy), >50.4 vs. ≤50.4	1.7 (0.3–7.1)	
Adjuvant chemotherapy, yes vs. no	1.5 (0.5–4.4)	

LN, lymph node; LND, lymph node dissection.

*Represents odds ratio for which $p<0.05$.

The presence of at least one tumor-positive pelvic lymph node was also associated with increased lymphedema risk (OR, 4.1; 95% CI, 1.4 to 12.3; $p=0.01$). Specifically, 4.3% of patients with negative pelvic lymph nodes developed lymphedema whereas 15.7% of patients with positive pelvic lymph nodes did. However, the presence of more positive lymph nodes did not increase the likelihood of lymphedema (OR, 1.08 per additional positive lymph node; 95% CI, 0.79 to 1.34). Of note, the presence of positive pelvic lymph nodes was not associated with an increased risk of disease recurrence after treatment ($p=0.40$).

A multivariate regression model was constructed to include lymph node positivity and lymph node dissection as possible predictors of lymphedema risk. In this model, lymph node positivity continued to exhibit a statistically significant association with lymphedema (OR, 3.2; 95% CI, 1.0007 to 10.7; $p=0.0499$) while the association of lymph-node dissection with lymphedema risk was no longer statistically significant ($p=0.27$).

Notably, in this population of patients with relatively high-risk endometrial cancer, including 43.4% ($n=92$) with stage III disease and 40.1% ($n=85$) with non-endometrioid histology, disease recurred in only 23.6% ($n=50$), with isolated pelvic recurrence occurring in only 1.4% ($n=3$).

DISCUSSION

This series found that patients who have at least one pathologically positive lymph node at diagnosis have a higher risk of lymphedema, even when controlling for pelvic lymph node dissection. While this observation has not been previously reported in studies of endometrial cancer, there is precedent in the breast cancer literature, where the number of positive axillary lymph nodes has been found to be associated with the risk of upper-extremity lymphedema, independent of the number of lymph nodes dissected [12]. In a study from Mayo Clinic where 591 endometrial cancer patients responded to a mail-in survey and 17% reported a diagnosis of lymphedema, the authors found an association between stage III–IV disease (vs. stage I–II disease) and lymphedema risk, though this did not hold up with multivariate analysis [8].

While the mechanism by which lymph-node positivity increases the risk of lymphedema is not known, recent molecular imaging techniques have shown that in the axilla, the presence of tumor cells in sentinel lymph nodes can impede lymphatic flow [13]. This observation suggests that the presence of tumor cells in the pelvic lymph nodes might also disrupt the normal lymphatic architecture, resulting in altered lymphatic drainage from the lower extremities. However, given that there is no association between disease recurrence and lymphedema risk, it seems unlikely that the mechanism by which lymph-node positivity predisposes patients to lymphedema is by serving as a nidus for disease recurrence, acting by mass effect to obstruct lymphatic flow. Rather, we hypothesize that the presence of tumor cells in the lymphatic space may cause irreversible changes to the extracellular environment, thereby altering the local architecture. The presence of positive pelvic lymph nodes likely increases the probability of microscopic tumor implants in the pelvic lymphovascular bed that were not observed during surgical staging. Adjuvant radiation may effectively kill these microscopic tumor cells leading to regions of lymphovascular fibrosis, further increasing the risk of lymphedema. The surprising observation that there is no association between pelvic lymph-node positivity and risk of disease recurrence likely speaks to the efficacy of adjuvant radiotherapy in treating even high-risk patients.

Several previous studies with conflicting results have investigated a possible association between radiation treatment and lymphedema. Some have suggested that postoperative radiotherapy increases the risk of lymphedema. Notably, however, the majority of patients in those studies had more than 20 nodes removed, which may be higher than typical of many institutions [4,6,8,14]. In contrast, neither van de Poll-Franse et al. [15], with a median of 13 nodes (range, 1 to 42 nodes) removed, nor Achouri et al. [5], with a mean of 12.0 nodes (standard deviation, 5.9) removed, found a relationship between adjuvant radiotherapy and lymphedema risk using either physician-reported or patient-reported outcome data. While all patients in our series received adjuvant radiation, the dose or length of treatment time did not have a significant effect on lymphedema rates.

While we found only a weak association of lymphedema with lymph-node dissection on univariate analysis, the average number of nodes dissected in our patient population is lower (mean, 9.7) than that of series reporting an increased association. For example, in two Japanese series with higher rates (27.2% to 37.8%) of lymphedema, 0.7% to 9.8% of patients received adjuvant radiation and more than 90% had 20 or more lymph nodes removed [4,6]. Interestingly, the few patients from the Japanese series with fewer than 10 lymph nodes removed had a lymphedema rate of only 10% [6]. In one series from Memorial Sloan-Kettering, the lymphedema rate was found to be 3.4% and was limited exclusively to women who had more than 10 lymph nodes removed [3]. Our current series reports a mean of 9.7 lymph nodes removed and a 7.1% lymphedema rate. Similarly, a report by Achouri et al. [5] found that in the context of a mean 12.0 lymph nodes removed, the lymphedema rate was 11.4%.

Given that in this series only 11.3% of patients had more than 20 lymph nodes removed, the less extensive dissection may account for the weaker association between dissection and lymphedema. By not having lymph node dissection be an overwhelming explanatory variable, this study is uniquely positioned to find the novel factor of nodal positivity influencing lymphedema risk. Despite the relatively limited lymph node dissection performed in this population of high-risk patients, the outcomes in terms of lymphedema (7%) and disease recurrence (23.6%) remained quite strong.

In this study, more than 50% of lymphedema cases (n=8) improved or resolved by 15 months. No association was found between documented interventions to treat the new-onset lymphedema and improvement or resolution of the symptoms. Notably, one-third of patients with lymphedema did not receive any intervention. Of those who did, most tried compression stockings.

The literature on lower extremity lymphedema treatment and its efficacy is not yet robust. A systematic review of the literature for secondary lower extremity lymphedema management in cancer patients was unable to reach any conclusions about best practice recommendations [16]. In general, the most commonly recommended intervention is compression stockings, which have shown some efficacy for decades [17-20]. However, more recent work has questioned whether class-II compression stockings have much effect [21]. Some studies suggest intermittent pneumatic compression may be more effective in mobilizing stagnant lymphatic fluid [18,22]. The best data seem to support complex decongestion therapy, but this intensive regimen of physical therapy, massage, and other adjuncts has significant resource demands and is not available to all patients [23-25]. The role of physical therapy for lower extremity lymphedema is not well defined. Various surgical interventions are also

possible, including lymphatico-venous anastomoses; however, given their invasive nature, these interventions are typically undertaken in only the most problematic and refractory cases [26,27]. Future studies into early and systematic implementation of interventions including exercise and compression devices in endometrial-cancer patients found to have lymph-node positivity may be effective in decreasing the burden of posttreatment lymphedema.

This analysis was performed on a retrospectively collected single-institution dataset; as such, the results and conclusions described are hypothesis-generating rather than definitive. In addition, it was not the practice at our institution during the period under review to formally measure the degree of lymphedema during patient visits despite the existence of multiple validated methods for doing so [28]. As a result, we relied on the documentation of physician- or patient-reported lymphedema after treatment. Similarly, the resolution, improvement or progression of lymphedema was recorded only as qualitatively reported by physician or patient and documented in the medical record. For this reason the precise numbers documented may be only an approximation of the “true” lymphedema rate and course. However, our study is not unique in this respect and it is reassuring that multiple prior studies of endometrial-cancer patients treated similarly to our own have reported very similar overall rates of lymphedema [3,5].

In conclusion, this study found that 7.1% of 212 endometrial-cancer patients receiving adjuvant pelvic radiotherapy with or without chemotherapy developed new-onset lower-extremity lymphedema after completion of treatment. The presence of at least one pathologically positive node at diagnosis was associated with an increased risk of lymphedema, even when controlling for pelvic lymph-node dissection. These findings are significant in suggesting that patients with stage III disease may benefit from more aggressive monitoring and potentially prophylactic measures to limit the risk of long-term lymphedema. However, future studies are needed to determine which such interventions are likely to be most effective and whether targeting their implementation to the highest risk groups will lower overall post-treatment lymphedema rates.

ACKNOWLEDGMENTS

Thank you to Barbara Silver for reviewing the manuscript.

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